ORIGINAL RESEARCH ARTICLE

Association Between Adverse Events and Discontinuation of Antiepileptic Drugs Among Drug-Naïve Adults with Epilepsy

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Abstract

Background Adherence to antiepileptic drugs (AEDs) remains the primary management tool to prevent recurrent seizures in patients with epilepsy. Adverse events associated with AEDs could have an impact on adherence and result in treatment failures.

Objective The goal of this study was to assess the association between adverse events and discontinuation of AEDs for AED-naïve patients with epilepsy. Our second objective was to estimate the economic burden of AED discontinuation.

Methods We retrospectively analyzed IBM MarketScan administrative data from 2014 to 2017. The cohort consisted of new users of AEDs with an epilepsy diagnosis and with two or more subsequent AED claims. Outpatient and inpatient cohorts were analyzed separately. Adverse events were identified by injury codes (E-CODES) or by *International Classification of Diseases, Ninth/Tenth Edition* (ICD-9/10) codes for disease manifestations reported in the literature or product inserts (LADE). Discontinuation of AEDs was defined as a gap of ≥ 60 days without a refill. All cost comparisons were based on 1:1 propensity-score matching. Associations between adverse events and discontinuation were estimated using logistic regression, adjusting for predefined covariates such as age, sex, Charlson Comorbidity Index, insurance type, and AED type.

Results The overall discontinuation rate was 9% (E-CODES rate was 0.1% and LADE rate was 27%). The discontinued group was older (56.1 vs. 52.8 years; $p < 0.0001$). Adults aged ≥ 65 years had the highest discontinuation rate (11%). Patients who discontinued had fewer AED claims (6.8 vs. 9.2; $p < 0.0001$), more outpatient claims (19.3 vs. 17.8; $p < 0.0001$), and longer hospital stays (6.6 vs. 5.3 days; $p < 0.0001$). Differences in daily outpatient costs between patients with and without adverse events were statistically significant (E-CODES \$US213 vs. 105; $p = 0.001$; LADE \$US188 vs. 161; $p < 0.0001$). Additionally, total cost of AEDs in the outpatient cohort was higher for patients with adverse events (E-CODES and LADE). There was no association between E-CODES and AED discontinuation; however, there was a positive association between LADE and discontinuation in the outpatient cohort but a negative association in the inpatient cohort.

Conclusion We found that total costs of prescriptions claimed and total costs of outpatient visits among the outpatient cohort were higher for those with adverse drug events than for those without. An association between adverse events and discontinuation was inconclusive because it depended on the target population and how the adverse events were identified.

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Key Points

Our investigation into an association between adverse drug events and discontinuation of antiepileptic drugs was inconclusive, and these results were influenced by how adverse events were identified.

Elderly patients discontinued antiepileptic drugs more frequently than did nonelderly patients.

Adverse drug events were associated with higher total costs of outpatient visits and total costs of antiepileptic drugs.

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1 Introduction

Epilepsy is a chronic neurological condition that affects approximately 3.4 million people in the USA [1]. Antiepileptic drugs (AEDs), the mainstay of epilepsy treatment, are generally effective, and 47% of people treated with their first prescribed AED experience seizure freedom [2]. In total, 28 US FDA-approved AEDs were available in the US market in 2019 [3]. Studies that assessed the efficacies of AEDs found no significant differences in treatment effect [4] and, although efficacy remains the primary determinant for AED selection, their safety/tolerability is an additional criteria that drives treatment selection [5].

Adverse events are defined as injuries from the use of drugs and could be the result of adverse drug reactions, medication errors, therapeutic failures, adverse drug withdrawal events, or overdoses [6]. Adverse events have long been recognized as a public health problem that increases healthcare resource utilization, with more than 1.3 million emergency room visits and over 350,000 hospitalizations per year according to the Centers for Disease Control and Prevention (CDC) [7]. For patients with epilepsy, studies suggest that adverse events lead to treatment failures and have a significant impact on their health-related quality of life [8]. There is some evidence to suggest that adverse events affect adherence and/or discontinuation of medications [9–11]. Discontinuation of AEDs is also associated with treatment failures, recurrence of seizures, AED ineffectiveness, and drug price [10, 12, 13]. The rate and severity of adverse events varies by drug and generation of the AED. Newer-generation AEDs have unique and diverse mechanisms of action that have improved their safety and tolerability profile compared with previous generation agents [14].

Real-world database studies on the association between adverse events and drug discontinuation are limited. The CDC lists older AEDs such as phenytoin and carbamazepine as more likely to be discontinued because of adverse events, but a new study from Iran also suggested that newer AEDs were associated with discontinuation [10]. The goal of this study was, first, to estimate the association between AED discontinuation and adverse events based on the type of AED and, second, to estimate the economic burden of AED discontinuation in the USA. It adds to the few studies on AED discontinuation due to adverse events by focusing on patients receiving monotherapy and by adding the economic burden of discontinuation and adverse events.

2 Methods

2.1 Data Description, Cohort, and Variable Definitions

This was a retrospective cohort analysis of AED-naïve adult patients with epilepsy who started an AED monotherapy regimen. We used IBM Commercial and Medicare MarketScan claims datasets (MarketScan) from 1 January 2012 to 31 December 2017. MarketScan, a family of linkable databases across inpatient, outpatient, and prescription drug utilization claims, consists of nearly 240 million unique patient claims since 1995 [15]. These databases capture physician visits, emergency room visits, hospitalization claims, and prescription drugs from employees and their dependents of large commercial employers and health plans across the USA. Because of the wide variation in costs and characteristics among patients with epilepsy, we analyzed patients with inpatient and/or outpatient claims as well as adherent and nonadherent patients separately [16].

The cohort consisted of adults aged ≥ 18 years with prescription claims for an AED and an epilepsy diagnosis-related medical claim (inpatient and/or outpatient) (Table 1). We required that the patients have continuous enrollment for the year before and the year of analysis. We defined a cohort of AED-naïve patients using a 2-year lookback, requiring no AED claims in the 2 years prior to the year of interest. Patients were excluded if they participated in a capitated health plan (in the cost analysis) as such patients would lack necessary cost data because of the different reimbursement model. Other criteria excluded patients with only one fill of an AED, patients receiving combination therapy, and patients with surgical claims. The final cohort, adjusted for negative claims, consisted of AED-naïve adult patients on AED monotherapy with only medical (nonsurgical) and pharmacy claims from 1 January 2014 to 31 December 2017.

AED-related adverse events were identified by either drug-injury codes (E-CODES) (Table 1) or by disease manifestation *International Classification of Diseases, Ninth/ Tenth Edition* (ICD-9/ICD-10) codes (diseases or symptoms listed in product inserts as severe or occurring in more than 10% of patients or by the literature; LADE). This method of using LADE includes common manifestations of adverse events, and this approach was used to improve our predictive values of adverse event coding as this is a known limitation of many studies that rely on disease manifestation coding or injury coding alone [17]. When using administrative data, adverse events can be documented in several ways: (1) by documenting the suspected medication causing the adverse event using "external injury codes" (i.e., E or Y codes); (2) by documenting a new diagnoses that may be caused by the drug using "disease manifestation codes"; and (3) by grouping an external injury cause code using the drug-related etiology with a disease manifestation code indicating the patient's diagnosis [17].

In this study, E-CODES could be at any diagnosis position, but the LADE was required to be a principal diagnosis as this was the most conservative measurement approach. Utilization was summarized as number of epilepsy-related events (admissions, outpatient visits, prescription claims)

Table 1 Codes used in defining epilepsy and adverse event cohorts, and classification of antiepileptic drugs

Variable	Type	Details
Epilepsy	ICD-9	345.4, 345.40, 345.41, 345.5, 345.50, 345.51, 345.7, 345.70, 345.71, 780.39
	ICD-10	G40.2, G40.0, G40.1, G40.5, R56.9
ADE	E-CODES	E850.1–E858.9, E930.0–E934.9, E935.1–E949.9, 357.6, 692.3, 693.0, 960.0–964.9, 965.02–969.5, 969.8–979.9
	LADE	999, 446, 288.3, 289.89, v62.84, 322.9, 977.9, 695.13, 695.15, 284.1, 288.5, 995.27, 213.01, 298.9, 345.8, 270, 780.2, 780.39, 288.3, 367.1, 365
AED	Old/first generation	Valproate sodium, ethosuximide, carbamazepine, primidone, phenobarbital, phenytoin
	Newer generation	Topiramate, zonisamide, felbamate, levetiracetam, lamotrigine, oxcarbazepine
		Rufinamide, ezogabine, vigabatrin, lacosamide, pregabalin, clobazam, eslicarbazepine, perampanel, brivaracetam

ADE adverse drug events, *AED* antiepileptic drugs, *E-CODES* adverse drug events defined by epileptic-specific injury codes, *ICD-9/10* International Classification of Diseases, Ninth/Tenth Edition, *LADE* adverse drug events defined by literature and product inserts

per calendar year. Methods for measuring adverse events include clinical surveillance, chart review, electronic medical record review, observation of patient care, or administrative claims data [14]. When administrative claims data are used, most studies either use injury codes (E-CODES) or disease manifestation codes (LADE) [18]. We used an administrative dataset in this study for the added benefit of access to cost of utilization data.

2.2 Outcomes of Interest

AED utilization was measured by adherence using proportion of days covered (PDC), by discontinuation rate using proportion of patients who discontinued the AEDs within 180 days, and by duration of therapy, calculated as days on AED (from index) to the day of discontinuation. PDC was calculated by dividing the total number of days of AED covered within the first 6 months (180 days) [19]. Discontinuation was defined by a gap of ≥ 60 days between the end of the days supplied on one AED claim and the date of fill of the next AED claim. A patient with this gap was considered to have discontinued the AED. Different gaps have been used to define discontinuation in the literature, including 30 and 90 days [20, 21]. We also estimated AED discontinuation, defined as gaps ≥ 30 days and ≥ 45 days.

Costs were summarized as patients' mean cost per event and total cost per calendar year adjusted to $US, year 2017 values, by the medical component of the consumer price index [20, 22] (Table 2). For subgroup analysis, we also looked at discontinuation rates and adverse events by type of AED. AEDs are classified into three generations based on their FDA approval date: first-generation AEDs were approved prior to the 1990s, second-generation AEDs were approved in the 1990s and third-generation AEDs in the 2000s. For this study, we classified first-generation AEDs as "old" and the second-/third-generation AEDs as "newer" (Tables 1 and 3) [23, 24].

2.3 Analysis

The analysis was guided by our two objectives: (1) to assess the association between discontinuation of AED and adverse events in this target population and (2) to characterize and estimate the economic burden of adverse events amongst AED-naïve patients with epilepsy on AED monotherapy. Descriptive statistics were used to summarize patient characteristics; frequencies, proportions, means, and medians were used according to the type of data (categorical or continuous variables) or whether the continuous variables were normally distributed. Bivariate analyses involved comparing patients who discontinued AEDs with those who did not and comparing patients with old AEDs with those with newer AEDs, using Chi-squared or Fisher's exact tests for categorical variables and Student's *t* test or the Mann–Whitney *U* test for continuous variables. For costs of outpatient visits, hospital admissions, and AED claims, we used propensity scoring methodology to match (1:1) those who discontinued therapy with those who did not and to match those with adverse events and those without. Matching was based on demographics such as age, sex, geographic location, epilepsy-specific Charlson Comorbidity Index (eCCI), number of outpatient visits, length of stay, and type of health plan, depending on the outcome of interest. Associations between discontinuation rate and adverse events of AEDs were assessed with logistic regression. Four different models were assessed: (1) model for inpatients with a focus on E-CODES; (2) model for inpatients with a focus on LADE; (3) model for outpatients with a focus on E-CODES; and (4) model for outpatients with focus on LADE. Statistical significance was defined as a *p* value <0.05.

Table 2 Costs of AEDs, outpatient visits, and admission by discontinuation and adverse event

Variable	Discontinuation (at 60 days)			LADE			E-CODES		
	Yes	No	SE	Yes	No	SE	Yes	No	SE
Outpatient									
Total cost of prescriptions filled	956	1086	148	1290	1250	39	1388	818	470
Total cost of outpatient claims/day	157	165	3.7	188	161	3.7	213	105	24
Total cost of outpatient claims/year	8847	11,093	990	17,051	11,988	764	23,255	6031	4158
Inpatient									
Total cost of prescriptions filled	412	439	71	453	480	77	318	465	141
Total cost of admission/year	22,936	21,913	1181	21,227	24,250	1603	22,111	24,248	5440

Costs presented in $US, year 2017 values

AEDs antiepileptic drugs, *E-CODES* adverse drug events defined by epileptic-specific injury codes, *LADE* adverse drug events defined by literature and product inserts, *SE* standard error

3 Results

3.1 Overall Cohort and Discontinuation Cohort Characteristics

Over the 4-year study period, about 1% of the 596 million outpatient claims were epilepsy related, and 0.8% were among adult patients aged ≥ 18 years. Similarly, about 7.1% of 1.8 million discharges were epilepsy related, and 4.9% were amongst adults aged ≥ 18 years. Our cohort consisted of 384,561 patients with outpatient and AED claims and 60,913 people with inpatient and AED claims.

3.1.1 Discontinuation

The overall AED discontinuation rates, based on a 60-day gap in therapy, were 9.1 and 9.2% in the outpatient and inpatient cohorts, respectively. The inpatient cohort was, on average, older than the outpatient cohort by over 10 years. The discontinued group was also older (outpatient mean age 54.2 vs. 50.9 years; inpatient mean age 67.6 vs. 64.8 years). Adults aged ≥ 65 years had the highest discontinuation rate in both inpatient and outpatient cohorts (Tables 3 and 4). More patients with adverse events discontinued their AED in the outpatient cohort. The percentage with any discontinuation was 31.2 vs. 29.2 ($p < 0.0001$) for LADE and 0.08 vs. 0.06 ($p = 0.1230$) for E-CODES. However, in the inpatient cohort, there was no difference in the proportion of E-CODES (0.2 vs. 0.2; $p = 0.5921$) but a lower proportion among patients with LADE (12.8 vs. 14.7; $p < 0.0001$). Additionally, the eCCI was higher for patients who discontinued (1.0 vs. 0.7; $p < 0.0001$) (Table 4).

3.1.2 Type of Antiepileptic Drug

The proportion of patients on the newer AEDs was higher in the inpatient cohort (75.8%) than in the outpatient cohort (69%). Among patients in the outpatient cohort, those on the newer AEDs were older (mean 53.5 vs. 50.2 years), but, among the inpatient cohort, those on the newer AEDs were younger than those on the older AEDs (mean 64.4 vs. 66.9 years). The proportion of patients with adverse events was mixed: for E-CODES, the proportion was higher among those on the old than on the newer AEDs (outpatient cohort 0.2 vs. 0.0; $p < 0.0001$; inpatient cohort 0.3 vs. 0.1; $p < 0.0001$), but, for LADE, the proportion was higher for the newer than the old AEDs (outpatient cohort 31.5 vs. 25.2; $p < 0.0001$; inpatient cohort 16.0 vs. 10.0; $p < 0.0001$). Patients on newer AEDs discontinued at a higher rate than those on the old AEDs (9.4 vs. 8.3; data not shown).

3.2 Economic Burden: Utilization and Cost

3.2.1 Discontinuation

As expected, the PDC, days covered, and numbers of prescriptions filled were lower in the discontinued than the not-discontinued group, for both inpatient and outpatient cohorts. In terms of utilization, those who discontinued had more outpatient visits (19.4 vs. 17.8; $p < 0.0001$) than those who did not discontinue. However, there was no difference in number of admissions, and those who discontinued had a longer length of hospital stay (mean 6.6 vs. 5.3 days; $p < 0.0001$) than those who did not discontinue. The total cost of outpatient visits was lower in the discontinued group ($US8847 vs. 11,093), and the total cost of inpatient admission was higher in the discontinued group ($US22,936 vs. 21,913) (Tables 2 and 5). Adherence was high for old and newer AEDs for both the inpatient (PDC 0.8) and the outpatient cohorts (PDC 0.9). The number of outpatient visits was higher with the old AEDs than the newer AEDs, but the number of admissions was the same (1.2 admissions/year for each) (Table 5).

Table 3 Outpatients with epilepsy on newly prescribed AEDs by discontinuation and type of AED

Variable and type	Discontinuation[a]			Antiepileptic drugs (by type)		
	Yes $N = 32{,}508$ (9.1%)	No $N = 327{,}053$ (90.9%)	p value	Old $N = 111{,}634$ (30.7%)	Newer $N = 252{,}513$ (69.3%)	p value
Age, years[b]	54.2 ± 19.4	50.9 ± 18.2	0.0000	50.2 ± 19.1	53.5 ± 16.3	0.0000
Age groups						
18–34 (20.8%)	18.4	21.1	0.0000	13.9	24.0	0.0000
35–44 (13.7%)	12.0	13.9		12.5	14.3	
45–54 (19.8%)	18.6	20.0		22.9	18.3	
55–64 (25.6%)	23.0	25.9		31.4	22.9	
≥ 65 (20.1%)	28.0	19.3		19.3	21.0	
Sex						
Female (56.2%)	56.8	56.2	0.0200	45.6	61.0	0.0000
Male (43.7%)	43.2	43.8		54.4	39.0	
Region						
North east (20.4%)	20.3	20.4	0.0000	20.1	20.4	0.0000
North central (23.1%)	28.4	22.6		23.8	22.8	
South (43.8%)	40.2	44.2		44.3	43.7	
West (12.5%)	10.8	12.7		11.6	12.9	
Unknown (0.2%)	0.2	0.2		0.3	0.2	
Insurance						
Comprehensive (12.2%)	17.4	11.6	0.0000	11.6	12.4	0.0000
EPO (0.8)	0.9	0.8		0.8	0.8	
HMO (9.2%)	7.5	9.3		8.8	9.3	
POS (5.5%)	4.5	5.6		5.7	5.3	
PPO (54.8%)	52.9	55.0		55.3	54.5	
POSWC (0.8%)	0.6	0.8		0.7	0.8	
CDHP (11.2%)	10.4	11.3		11.7	11.0	
HDHP (5.6%)	5.8	5.6		5.2	5.8	
ER Visit: yes	3.1	2.8	0.0002	2.1	3.2	0.0000
LADE: yes	31.2	29.2	0.0000	25.2	31.5	0.0000
E-CODES: yes	0.08	0.06	0.1230	0.2	0.0	0.0000

AEDs antiepileptic drugs, *CDHP* consumer-driven health plan, *E-CODES* adverse drug events defined by epileptic-specific injury codes, *EPO* exclusive provider organization, *HDHP* high-deductible health plan, *HMO* health maintenance organization, *LADE* adverse drug events defined by literature and product inserts, *POS* point-of-service, *POSWC* point-of-service with capitation, *PPO* preferred provider organization, *SD* standard deviation

[a]Based on 60-day gap in therapy

[b]Presented as mean $\pm$ standard deviation unless otherwise indicated

3.2.2 Adverse Drug Events

The total costs of prescriptions filled and outpatient visits were higher among those with adverse events (LADE and E-CODES) than in those without in the outpatient cohort. However, the total costs of prescriptions filled and admissions were lower for those with adverse events (LADE and E-CODES) than those without (Table 2). In total, 86% of the AED claims were multisource generics (mean $US489 ± standard deviation 1209; median $US189), 8.5% were multisource brands where generics were available (mean $US5882 ± 7346; median $US7346), 3.5% were single-source brands (mean $US7951 ± 11,083; median $US7496), ~ 2% were single-source generics (mean $US2574 ± 3234; median $US1490), and the rest were multisource brands (mean $US29,142 ± 49,569; median $US2885; results not shown).

3.3 Association Between Discontinuation and Adverse Events

The proportion of patients with E-CODES in the discontinued group was higher (0.08 vs. 0.06; $p = 0.1230$) in the outpatient cohort but the same in the inpatient group (0.2 vs. 0.2; $p = 0.5921$) (Tables 3 and 4), meaning no significant

Table 4 Inpatients with epilepsy on newly prescribed AEDs by discontinuation and type of AED

Variable	Discontinuation[a]			Antiepileptic drugs (by type)		
	Yes N = 5443 (9.2%)	No N = 53,521 (90.8%)	p value	Old N = 14,712 (24.2%)	Newer N = 46,201 (75.8%)	p value
Mean age, years[b]	67.6 ± 17.8	64.8 ± 18.5	0.0000	66.9 ± 18.3	64.4 ± 18.5	0.0000
Age groups, years						
18–34 (7.5%)	6.0	7.7	0.0000	7.3	7.7	0.0000
35–44 (5.7%)	4.5	5.9		4.4	6.1	
45–54 (12.3%)	10.1	12.5		10.3	12.9	
55–64 (23.1%)	21.6	23.1		22	23.5	
≥ 65 (51.5%)	57.8	50.8		56.0	49.8	
Sex						
Female (56.1%)	58.8	55.8	0.0000	49.5	58.1	0.0000
Male (43.9%)	41.2	44.2		50.5	41.9	
Region						
North east (22.5)	22.8	19.3	0.0000	20.0	23.2	
North central (31.6)	30.9	38.1		35.0	30.4	
South (35.2)	35.3	34.0		32.9	36.0	
West (10.1)	10.3	7.8		11.5	9.7	
Unknown (0.7)	0.7	0.7		0.7	0.7	
Insurance						
Comprehensive (30.4%)	36.7	29.8	0.0000	34.6	29.0	0.0000
EPO (0.5)	0.7	0.5		0.5	0.5	
HMO (9.5%)	8.1	9.6		10.3	9.2	
POS (5.2%)	4.1	5.3		4.2	5.5	
PPO (46.7%)	44.3	46.9		43.9	47.6	
POSWC (0.5%)	0.7	0.5		0.6	0.5	
CDHP (5.1%)	4.3	5.1		3.9	5.5	
HDHP (2.1%)	1.2	2.2		2.0	2.1	
LADE: yes	12.8	14.7	0.0001	10.5	16.0	0.0000
E-CODES: yes	0.2	0.2	0.5921	0.3	0.1	0.0001
CCI[b]	0.4 ± 0.8	0.4 ± 0.7	0.0010	0.4 ± 0.7	0.4 ± 0.8	0.4720
eCCI[b]	1.0 ± 1.4	0.7 ± 1.2	0.0000	0.7 ± 1.2	0.8 ± 1.3	0.0000

AED antiepileptic drugs, *CDHP* consumer-driven health plan, *E-CODES* adverse drug events defined by epileptic-specific injury codes, *EPO* exclusive provider organization, *HDHP* high-deductible health plan, *HMO* health maintenance organization, *LADE* adverse drug events defined by literature and product inserts, *POS* point-of-service, *POSWC* point-of-service with capitation, *PPO* preferred provider organization, *SD* standard deviation

[a]Based on 60-day gap in therapy

[b]Presented as mean ± standard deviation unless otherwise indicated

association between E-CODES and discontinuation was found. After controlling for demographics in the logistic regression, there was still no significant association in both outpatient (− 0.2747; $p = 0.233$) and inpatient cohorts (0.2195; $p = 0.477$) (Table 6). For patients with both outpatient and inpatient epilepsy claims, the odds ratio (OR) of AED discontinuation due to E-CODES (not shown) was 2.7 times higher ($p = 0.025$) than for those who did not have an adverse event. In contrast, the proportion of patients with LADE in the discontinued group was higher (31.2 vs. 29.2; $p < 0.0001$) in the outpatient cohort and lower in the inpatient cohort (12.8 vs. 14.7; $p < 0.0001$). These associations remained statistically significant after controlling for demographics in the logistic regression models (outpatient 0.0395; $p = 0.003$; inpatient − 0.1367; $p = 0.002$). The following variables had a positive association with AED discontinuation: age, number of outpatient visits, number of inpatient admissions, length of hospital stay, and number of comorbidities. For example, the older the patient, the more likely they were to discontinue the AED, or the more

Table 5 Utilization of healthcare resources of patients with epilepsy on AEDs by type and discontinuation

Variable	Discontinuation (at 60 days)			Antiepileptic drugs (by type)		
	Yes (N = 32,508)	No (N = 327,053)	p value	Old (N = 111,634)	New (N = 252,513)	p value
Outpatients						
PDC	0.7 ± 0.3	0.9 ± 0.1	0.0000	0.9 ± 0.2	0.9 ± 0.2	0.0000
Days of AED covered over 180 days	123.8 ± 50.1	161.2 ± 26.4	0.0000	159.8 ± 29.6	157.0 ± 31.9	0.0000
Prescription claims (N)	6.8 ± 4.3	9.4 ± 5.2	0.0000	9.2 ± 5.5	8.9 ± 5.1	0.0000
Outpatient visits per year (N)	19.4 ± 26.2	17.8 ± 24.1	0.0000	18.6 ± 22.9	17.7 ± 25.0	0.0000
Inpatients						
PDC	0.6 ± 0.3	0.8 ± 0.2	0.0000	0.8 ± 0.2	0.8 ± 0.2	0.0000
Days covered	100.2 ± 46.9	150.2 ± 34.4	0.0000	149.1 ± 36.6	144.5 ± 39.1	0.0000
Prescription claims (N)	7.2 ± 5.5	8.6 ± 4.7	0.0000	9.2 ± 5.7	7.9 ± 4.6	0.0000
Admissions (N)	1.2 ± 0.6	1.2 ± 0.5	0.0000	1.2 ± 0.5	1.2 ± 0.5	0.7490
Hospital los (days)	6.6 ± 10.0	5.3 ± 7.2	0.0000	5.2 ± 6.4	5.5 ± 7.9	0.0000

Data are presented as mean ± standard deviation unless otherwise indicated

AED antiepileptic drugs, *LOS* length of stay, *PDC* proportion of days covered (a measure of drug adherence), *SD* standard deviation

comorbidities the patient had, the more likely they were to discontinue the AED. Additionally, females were more likely to discontinue their AEDs than males, and—in the outpatient cohort—those on old AEDs were more likely to discontinue than those on newer AEDs, but this pattern was not seen in the inpatient cohort (Table 6).

4 Discussion

4.1 General Comments

This retrospective claims-based analysis sought to estimate the association between adverse drug events and discontinuation of AEDs and to update the economic burden of AED discontinuation among AED-naïve patients with epilepsy on AED monotherapy, within a cohort of patients with commercial health plans, including Medicare Advantage.

We found no association between E-CODES and discontinuation except in a subset of patients with both inpatient and outpatient claims. The association between LADE and discontinuation is mixed, with a positive association between LADE and discontinuation in the outpatient population but a negative association in the inpatient population. There are several reasons why patients with epilepsy discontinue or withdraw from taking an AED. Giussani et al. [13], in an Italian study, listed the top three reasons as terminal remission, ineffectiveness, and adverse events. In that study, withdrawal (discontinued) due to adverse events was 0.5% at year 1 and 3.3% at year 20, so our E-CODES findings were lower (0.2% in inpatients and 0.08% in outpatients). A higher proportion of our cohort could have discontinued because of terminal remission or ineffectiveness of their

AED. Terminal remission is not recommended less than 2 years into therapy because of an increased risk of recurrent seizures [25]. These results suggest that an association between adverse events and AED discontinuation was based on how the adverse events were identified and the target population analyzed. When adverse events were identified as E-CODES and the target population were patients with both inpatient and outpatient claims, the odds of AED discontinuation were 2.7 times higher than for those who did not discontinue their AEDs. E-CODES are external injuries specific to AEDs, whereas LADE, based on the literature and product inserts, tend to lack specificity and include diseases such as pneumonia and symptoms such as nausea and vomiting. Although specificity is high for E-CODES, studies suggest they are underreported [8]. There was no statistically significant association between E-CODES and AED discontinuation when the target population comprised patients with only outpatient or only inpatient claims. This could be because of the small proportion of E-CODES amongst such claims. On the other hand, the lack of specificity with LADE could explain the negative association amongst those with inpatient claims but a positive association amongst those with outpatient claims.

In our cohorts, we found a discontinuation rate of about 9% in both cohorts. The adherence (PDC) within 6 months was high in our cohort, with a mean of 0.8 for inpatients and 0.9 for outpatients. This is similar to the PDC of 0.85 reported by Joyce et al. [26], who also used a Truven MarketScan dataset. Discontinuation rates amongst patients taking old versus newer AEDs were similar and below 10%. This is similar to the rate reported by Giussani et al. [13] in Italy for the first-year use of AEDs. Older adults, who often use the old AEDs, have a higher discontinuation rate, most

Table 6 Four logistic regression models of association between AED discontinuation and adverse events

Variables	Outpatient population (N = 355,062)				Inpatient population (N = 57,922)			
	E-CODES		LADE		E-CODES		LADE	
	Coeff.	p value	Coeff.	p value	Coeff.	p value	Coeff.	p value
Adverse drug event	− 0.2747	0.233	0.0395	0.003	0.2195	0.477	− 0.1367	0.002
Age	0.0005	0.000	0.0005	0.000	0.0054	0.000	0.0053	0.000
Sex (male)	− 0.0411	0.001	− 0.4139	0.001	− 0.1456	0.000	− 0.1482	0.000
No. of OPD visits	0.0039	0.000	0.0038	0.000	–	–	–	–
Emergency room visit	0.0817	0.019	0.0704	0.045	–	–	–	–
No. of prescriptions claims	− 0.1345	0.000	− 0.1345	0.000	− 0.0704	0.000	− 0.0708	0.000
No. of admissions	–	–	–	–	0.0949	0.000	0.1032	0.000
Hospital length of stay	–	–	–	–	0.0111	0.000	0.0107	0.000
eCCI	–	–	–	–	0.1402	0.000	0.1384	0.000
Comprehensive[a]	0.1207	0.000	0.1184	0.000	0.1508	0.052	0.1472	0.058
EPO	0.2049	0.002	0.2046	0.002	0.4652	0.017	0.4612	0.018
HDHP	0.0780	0.011	0.0779	0.012	− 0.4102	0.005	− 0.4131	0.005
HMO	− 0.1338	0.000	− 0.1337	0.000	− 0.0388	0.653	− 0.0433	0.616
POS	− 0.1594	0.000	− 0.1592	0.000	− 0.1653	0.095	− 0.1660	0.093
POSWC	− 0.2136	0.006	− 0.2158	0.006	0.5743	0.003	0.5798	0.003
PPO	− 0.0124	0.538	− 0.0135	0.506	0.0538	0.461	0.0523	0.474
North east (region)[b]	− 0.1650	0.000	− 0.1656	0.000	− 0.2893	0.000	− 0.2848	0.000
South	− 0.1896	0.000	− 0.1890	0.000	− 0.1499	0.000	− 0.1482	0.000
West	− 0.2921	0.000	− 0.2914	0.000	− 0.3852	0.000	− 0.3842	0.000
Unknown	− 0.1259	0.302	− 0.1259	0.302	0.0595	0.726	0.0607	0.721
Type of AED (old generation)[c]	− 0.1569	0.000	− 0.1546	0.000	0.0413	0.227	0.0352	0.304

AED antiepileptic drug, *eCCI* epilepsy-specific Charlson Comorbidity Index, *E-CODES* adverse drug events defined by epileptic-specific injury codes, *EPO* exclusive provider organization, *HDHP* high-deductible health plan, *HMO* health maintenance organization, *LADE* adverse drug events defined as identified in the literature/product insert, *OPD* outpatient department, *POS* point-of-service, *POSWC* point-of-service with capitation, *PPO* preferred provider organization

[a]Insurance: all insurance variables compared with consumer-driver health plan

[b]Region: compared with north central region

[c]Generation: compared with newer-generation AED

likely because they have a higher eCCI score. Patients with higher eCCI scores had a higher discontinuation rate.

Nonadherence to medications was associated with increased use of some healthcare resources, including unplanned care. Several medication therapy management studies suggest the economic benefit of improved adherence [27]. Although we did not find a strong association between adverse events using administrative claims data, we did observe that adverse events could be costly among the users of new monotherapy AEDs in our cohort (i.e., increased outpatient visits/costs and emergency room visits among these users). In terms of cost, outpatient costs were higher for those who had adverse events but lower for those who discontinued. Although patients who discontinued had a higher number of outpatient visits and longer hospital stays, their outpatient and admission costs were lower than those who did not discontinue their AEDs. As mentioned earlier, there are several reasons for AED discontinuation beyond adverse events. Further research is needed to understand these associations.

4.2 Limitations

Some limitations of our study are worth mentioning. This was a retrospective analysis, so we do not claim causality. Because we used administrative claims data that were collected for reimbursement and not for research purposes, opportunities for miscoding of events do exist. E-CODES are commonly used in adverse event research, and underreporting has been reported in such studies [15, 17], yet LADEs lack specificity and are likely to overreport adverse events. A Canadian study on the validity of administrative data use in reporting adverse events in two tertiary care emergency departments estimated a low sensitivity of 6.8%, which increased to 28.1% when the definition was broadened to include codes indicating very likely, likely, or possible

adverse events [28]. Additionally, our dataset was limited to only commercial claims, including Medicare Advantage, but did not include Medicaid or other government programs such as Tricare and Veterans Affairs. However, this administrative dataset provided the opportunity to estimate burden at the same time as cost.

5 Conclusion

We found that total costs of prescriptions claimed and outpatient visits among the outpatient cohort were higher for those with adverse drug events than for those without. The association between adverse events and discontinuation was inconclusive because it depended on the target population and how the adverse events were identified. For monotherapy, medication adherence was high within the first 180 days, irrespective of the generation of AEDs used, but older patients—who often use the old AEDs—were more likely to discontinue their AEDs.

Declarations

Conflicts of Interest Michelle Vu and Tuong-Vi T. Huynh have no conflicts of interest that are directly relevant to the content of this article. They were research students of Samuel Peasah during the project. Samuel Peasah received funding from UCB for this project. Derek Ems and Silky Beaty are employees of UCB Inc. Jesse Fishman was an employee of UCB for a significant part of the project.

Ethics approval This study was exempt by Mercer University IRB.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data sharing is subject to IBM policy.

Code availability Not applicable.

Author Contributions The original concept was proposed by SKP with assistance from JF. SKP wrote the proposal with assistance from JF and MV. SB, DE, and JF supported SKP with data acquisition, study design, and analysis. SKP managed the project with assistance from DE and T-VTH. SKP wrote the article and it was reviewed and approved by all co-authors.

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